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New Approaches in the Treatment of Opioid Dependency During the Pregnancy.

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1. The Challenges of Methadone Pharmacotherapy in the Treatment of Pregnant Opioid Dependent Women

Loretta Finnegan

The chaotic lives of drug dependent women and the frequent lack of consistent prenatal care places them at increased risk for many medical problems and obstetrical complications during pregnancy. The complexity of the medical problems in the pregnant drug abuser is mirrored in the attendant psychosocial problems seen in this population. Drug-dependent and alcohol-using women often manifest anxiety, depression, and low self-esteem. Many addicted women share a history of past and current physical abuse and sexual assault. The complex matrix of intertwining medical and psychosocial risk factors that usually characterize illicit drug use during pregnancy dictate that a successful outcome can best be obtained within a comprehensive, supportive, non-judgmental environment that focuses on the multidimensional needs of the woman. This offers a unique opportunity to restructure the woman's life in a positive direction. In addition to the latter interventions, pharmacotherapy with methadone is indicated in most opioid dependent women. See Figure 1 which lists a recommended schema for comprehensive treatment of the drug dependent pregnant and post partum woman and her newborn/child.

Although methadone maintenance therapy has been used in pregnant women for over 40 years, no randomized trials comparing dosing regimens have been published on which to base specific therapeutic recommendations. It has been recommended that dosages should be individually determined which will keep the woman and fetus subjectively comfortable and clinically stable. Although the health and comfort of the pregnant opioid dependent woman remain paramount considerations, higher dosages of methadone (60-150 mg/day) early in pregnancy have been reported to be associated with more normal fetal growth. Data on the relationship between maternal methadone doses, especially late in pregnancy, and subsequent severity of neonatal abstinence have been variable causing considerable confusion for clinicians involved in treating these women. The development of neonatal abstinence has precipitated much controversy and emotional reactions by parents and medical staff. Studies have shown the variability of methadone pharmacokinetics in pregnant women in comparison to non-pregnant individuals. Plasma methadone levels during pregnancy show marked intra-patient and inter-patient variability and usually

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are somewhat lower than those prior to pregnancy. This decrease can be explained by an increased fluid space, a large tissue reservoir, and altered drug metabolism by the placenta and fetus. These data suggest that pregnant women may need increasing methadone doses during gestation and that lowering the dosage in an attempt to minimize neonatal abstinence would be medically inappropriate. During labor, the patient can be managed like any other parturient and conduction anesthesia should commence as early as possible.

In summary, perinatal opioid dependence is a problem of major public health importance for women and children throughout the world. Societal moral attitudes which have stigmatized and dehumanized women who use drugs during pregnancy have placed barriers in the way of obtaining optimal medical and obstetric care. These considerations apply to women of all races and socioeconomic status. The best public health result can be obtained once these barriers have been removed and women are provided appropriate services in a supportive, multidimensional treatment facility with the addition of well managed pharmacotherapy.

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2. Buprenorphine in the Treatment of Opioid Dependent Pregnant Women

Bernadette Winklbaaur and Gabriele Fischer

Continuous abuse of illicit opioids during pregnancy is associated with adverse consequences for mother, fetus and neonate [1] The main risk factor originates in the fluctuation of opioid concentration in the maternal blood, which may lead to withdrawal symptoms in the neonate as well as to symptoms of overdose. In addition, heroin use in pregnancy is often related to difficult psychosocial environmental conditions, malnutrition of the pregnant women and subsequently poor outcome in newborns.

Methadone maintenance of pregnant opioid dependent women has been found to reduce complications of pregnancy and childbirth, and leads to improved neonatal outcome [2]. However, methadone maintenance during the course of pregnancy is associated with potential side effects. Based on recent findings its administration appears to alter fetal activity and heart rate [3,4]. Moreover, neonatal abstinence syndrome (NAS) frequently occurs following methadone exposure.

With the increased propagation of buprenorphine treatment in opioid dependent patients, supportive data for this agent has been published consecutively. However, most trials on maintenance treatment of opioid dependence exclude pregnant women by definition, since these patients require specialized treatment programs in order to minimize potential harm to the fetus. Although data from more than 500 neonates prenatally exposed to buprenorphine have been published with no related physical teratogenic effects and a low rate of prematurity [5], it has to be emphasized that this findings are limited due to several possible confounding factors: in many cases results are based on retrospective data, the use of concomitant consumption of other substances is rarely reported in detail, no appropriate control groups or different NAS scoring systems used. Until today the majority of information has been gained through French publications, where buprenorphine has been available for more than 10 years. As a result of their office-based prescription policy, many pregnant patients in France have been treated with buprenorphine. These mainly naturalistic data indicate the safe use of buprenorphine in pregnant opioid dependent women [6,7,8,9]. However, to date limited data from prospective open-label controlled studies of neonates born to buprenorphine-treated mothers are available.

The first open-label, flexible-dosing, study on buprenorphine during pregnancy was carried out by Fischer et al. [10]. Overall 15 opioid-dependent pregnant women have been included; based on their findings buprenorphine was well tolerated during induction and mean birth outcome measures were within normal range. In eight of the neonates no NAS was observed, while mild NAS occurred in four and moderate symptoms, requiring treatment, in three cases. The mean duration of NAS

treatment was 1.1 days. A case report by Schindler et al. analyzed 2 buprenorphine-maintained pregnant women in a prospective manner and found both newborns to be healthy, not requiring NAS treatment [12].

Until now, there have been only two prospective double-blind, double-dummy randomized controlled trials comparing buprenorphine with methadone in pregnancy. Both studies, one from Europe and one from the US, used similar methodology to show the safety and comparability of both substances. The study by Jones et al investigated 18 pregnant opioid dependent women [12]. Based on their results buprenorphine was at least comparable to methadone in regard to maternal and neonatal outcome measures with some items in favour of buprenorphine: The total amount of opioid agonist medication for the treatment of NAS in methadone-exposed neonates was three times greater than for those prenatally exposed to buprenorphine. In addition, a significantly shorter hospital stay was found in the buprenorphine exposed group. In terms of peak NAS total scores or neonatal birth weight, no significant differences between the groups have been revealed. In order to minimize possible confounding effects of concomitant drug use, patients received voucher payments (“contingency management”) in return for negative urine samples and negative ethanol-breath samples. As a consequence, both groups had low rates of illicit drug consumption prior to delivery.

Fischer et al. included 18 opioid dependent pregnant women into a clinical trial, using as well a double-blind double-dummy design [13]. The mean methadone dose was 47.5 mg, and 13.5 mg per day for buprenorphine, whereas doses were slightly increased during the last trimester (+ 5 mg for methadone, + 0.5 mg for buprenorphine). In regard to neonatal outcome no significant differences between both groups were found. Overall 43% of the neonates did not require NAS treatment. NAS occurred 12 hours later (mean) in the buprenorphine group, while the mean duration of NAS treatment was 4.8 days for those babies born to buprenorphine maintained mothers and 5.3 days in the methadone group. No difference has been observed with respect to the dose of medication needed to manage NAS. As eight women of the buprenorphine versus six of the methadone group completed the study, the retention rate was somewhat higher in the buprenorphine group. Methadone, however, was significantly more effective in preventing concomitant opiate consumption, while both groups showed low concomitant consumption of cocaine and benzodiazepines.

Based on preliminary data, it appears that buprenorphine induces a milder withdrawal syndrome in newborns, compared to methadone [14]. The onset of NAS is usually observed within the first 12 to 72 hours after delivery reaching its maximum within approximately 66 to 96 hours, lasting approximately 120 to 168 hours, although considerable individual variability occurs. To date, only one paper reports a correlation between buprenorphine

dose and the severity of NAS [15]. This finding, however, was based on the maximum Lipsitz score, while most publications on NAS refer to the Finnegan score [16]. More recent reports [6,12,13] did not find a correlation. Further investigations are needed in that regard.

A recent comparative, multicenter clinical trial on the comparison of high-dose buprenorphine versus methadone maintenance in 259 pregnant women reported no major difference in perinatal prognosis. Based on their results a higher level of prematurity in the methadone group was found, which could also be explained by other confounding factors. In addition the mean onset of NAS for the methadone group was 81 h versus 66 h for the buprenorphine group [6].

Another recent prospective study by Ebner et al [17] aimed at the comparison of three neonatal groups being prenatally exposed to either methadone, buprenorphine or slow-release morphine with no concomitant consumption. Overall sixty percent of newborns required treatment for NAS: 68% in the methadone-exposed group, 82% in the morphine-exposed group and 21% in the buprenorphine-exposed group. As a result, a significantly lower incidence of NAS appearance was observed in the buprenorphine group compared to the other groups.

However, large randomized clinical trials in pregnant opioid dependent women are indispensable in order to document safety and efficacy, as currently both medications, methadone and buprenorphine, are classified as FDA pregnancy category C medications [5].

As a consequence, a new multi-site study has been designed. This large randomized double-blind, double-dummy study comparing the efficacy of buprenorphine to methadone treatment is still going on, whereas first results are currently published [18]. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project is an eight-site randomized, double-blind, double-dummy, flexible dosing and parallel group clinical trial hypothesizing that buprenorphine may lead to superior neonatal outcome. This study will also address research questions in regard to the influence of pregnancy on pharmacokinetics and pharmacodynamics of both, buprenorphine and methadone.

Conclusion

Over the past years an increasing number of results in favour of buprenorphine have been published emphasizing that NAS after intrauterine buprenorphine exposure might be less severe than that of methadone exposed newborns. However, further research is required to support these early findings which are limited to some extent due to several methodological flaws. Future investigations have to consider concomitant consumption, as, for example, nicotine dependence in opioid dependent pregnant women seems to be connected with smaller babies for gestational age-factors, compared to opioid dependence alone. Furthermore, concomitant consumption of illicit substances

influences neonatal outcome and may be reduced by contingency management. In general, monetary vouchers given to patients as reward for opioid- and cocaine-negative urines have been found to be successful. Pregnancy provides a perfect model for the use of this behavioural intervention as contingency management is provided for a limited time-course throughout pregnancy in a highly motivated group [19].

However, a novelty in the field of pharmacological studies in opioid dependent pregnant women is the multi-site, MOTHER trial, which might serve as a role model for future medication trials in this field of research.

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3. Comprehensive Treatment for the Pregnant Opioid Dependent Women: Traditional Approaches and the New

May Olofsson

Children born of mothers using alcohol or drugs in pregnancy are at high risk of developmental disturbances, neglect and abuse. These infants are at risk of birth defects, premature deliveries, low birth weight, perinatal death, asphyxia, brain damage, neonatal withdrawal symptoms (NAS), fetal alcohol syndrome (FAS) and other neonatal morbidity. Furthermore, these children are often growing up under bad circumstances with deprivation, neglect and abuse, which may enhance the consequences of the congenital damages in the development of these children. The children are normal from the very beginning of foetal life and have the potential for normal development if they are not exposed to drugs and other detrimental risk factors during foetal life. On that background, all the above mentioned complications for the children can be prevented if their mothers are provided with counselling, comprehensive treatment and support during pregnancy, delivery and the first years of the infants' life. Experience from USA and Denmark has shown that all the above mentioned complications for the children can be prevented by multidisciplinary, comprehensive prenatal and postnatal care. The risk for the children is a combination of their mother's health, her life situation and her lifestyle, including her consumption of alcohol, tobacco and drugs (Table 1).

Family Center at the University Hospitals of Copenhagen, Hvidovre Hospital and Rigshospitalet, is a specialized multidisciplinary department for alcohol and drug using pregnant women and their children up to the age of 6 years. The program was inspired by Family Center at Thomas Jefferson University Hospital in Philadelphia, USA, and by Dr. Loretta Finnegan's research and treatment methods. Family Center in Copenhagen offers comprehensive prenatal care, counselling, outpatient and inpatient treatment, opioid agonist therapy with methadone, psychosocial support, outreach, induced abortion and contraception (Table 2). After delivery, the infants are examined and treated in the neonatal department if they are suffering from neonatal abstinence syndrome (NAS) or other neonatal morbidity. Family Center is using Loretta Finnegan's method for the treatment of NAS. The mothers are inpatients as long as their infants need special care and the early attachment between mother and infant is supported. Table 3 lists the disturbances of early mother-infant attachment. From the beginning of pregnancy, Family Center collaborates with the Social Authorities and other professionals in the community so that the infants are provided with all the care, treatment and support that they need during the first years of life. After discharge from the hospital, the children are followed in Family Center including health care and developmental assessment in continued collaboration

Table 1. Risk factors of Pregnant Drug-Dependent Women
THE CONSTITUTION OF THE WOMEN Poor background, low self-esteem, distrust, poor education, emotional disturbances, psychopathology
SOCIAL PROBLEMS Poor housing, poor economy, prostitution, criminality, violence, imprisonment, drug-addicted partner, neglected children
THE HEALTH Poor nutrition, anaemia, infectious diseases
PHARMACOLOGIC/TERATOGENIC Alcohol, cocaine, opioids, amphetamine, tranquilizers, analgetics, cannabis, tobacco, caffeine, etc.
FLUCTUATION IN LEVEL OF DRUGS IN THE BLOOD Overdose, withdrawal symptoms
NEGLECT OF PRENATAL CARE Late detection of pregnancy, uncertain gestational age, neglect of health and prenatal care
PROCEDURES IN REFERRING TO PRENATAL CARE Bureaucratic procedures delay contact to prenatal care for women with alcohol-and drug problems

Table 2. Family Center of Copenhagen
Early intervention in pregnancy
Outreach work
In-patient and out-patient treatment
Prenatal care
Psycho-social support
Medical substitution therapy during pregnancy
Methadone-maintenance during pregnancy or detoxification
Treatment of NAS infants as per Finnegan NAS Score
Support of mother-infant attachment
Collaboration with Social Authorities and others
Follow-up of the children until 6 years of age
Counselling about HIV, hepatitis, abortion, etc.
Contraception

Table 3. Disturbances of Early Mother-Infant Attachment	
The Mother:	The Newborn:
1. Anxious about the infant's prognosis	1. Premature
2. Anxious about the social authorities	2. Low birth weight
3. Sense of guilt	3. Asphyxia
4. Intoxification	4. Infections
5. Withdrawal symptoms	5. Withdrawal symptoms
6. Difficulties in relationships	6. Medication
7. Low self-esteem	7. Separated from the mother
8. Depression	8. Other neonatal problems
9. Ambivalence	
10. Problems with paternity	
11. Social problems	
12. Lack of breast-feeding	
13. Separation from the infant in the hospital	

Table 4. Pregnant Women in Family Center 2003 – 2006 (N = 288)	
	N (%)
Alcohol	43 (15)
Cannabis	71 (25)
Cocaine	10 (3)
Opioids	115 (40)
Tranquilizers	49 (17)

with the Social Authorities. Some of the infants are discharged to their own home with their mother, some to a foster family with or without their mother, and some of the infants are discharged to a residential placement with or without their mother.

During the years 2003 – 2006, 288 pregnant women were referred to Family Center (Table 4). 115 were

	N (%)
Methadone Treatment	110 (95.7)
Buprenorphine Treatment	2 (1.7)
Without Medical Substitution	3 (2.6)
Detoxified to 0	32 (28%)
Detoxified to a lower dose	41 (37%)
Maintained on the same dose	39 (35%)

Birth weight	3127 Grams (885-4050)
Birth length	50 cm (40-53)
Head Circumference	34 cm (26-38)
Gestational Age	38 weeks (24-42)
Premature (<37 weeks)	10 (9%)
Low Birth weight (<2500 grams)	12 (14%)
NAS	72 (63%)

	N (%)
Home with the mother	30 (26%)
Residential care with the mother	22 (19%)
Residential care without mother	22 (19%)
Foster family with the mother	9 (10%)
Foster family without the mother	29 (25%)

dependent on opioids. 110 of these women were treated with methadone during pregnancy (Table 5). Table 6 shows the neonatal data and Table 7 shows the discharge status of the infants.

Family Center has reduced the number of children

suffering from congenital damages, low birth weight, premature delivery, perinatal asphyxia, NAS and other neonatal morbidity. Most of the children are growing up under stable home environments and are seen by pediatricians and child psychologists in Family Center. The

	%
PREMATURE BIRTH	20
LOW BIRTH WEIGHT	31
PERINATAL ASPHYXIA	20
NEONATAL WITHDRAWAL SYMPTOMS	85
IMPAIRED PSYCHOMOTOR DEVELOPMENT	21
BEHAVIOURAL AND EMOTIONAL DESTURBANCES	54
NORMAL DEVELOPMENT	25

1. Pregnant women are coming earlier into prenatal care (counselling about abortion, hepatitis, HIV, etc.)
2. The perinatal health of infants is improved (the number of premature and low birth weight infants and infants with asphyxia are reduced).
3. Reduction in NAS (Neonatal Abstinence Syndrome).
4. Reduction in FAS and other ARBD
5. Reduction in developmental disturbances, neglect and abuse
6. Infants are discharged to stable home environments.
7. The infants are followed-up by professionals during infancy. Developmental problems, neglect and abuse are prevented.
8. The mothers receive contraception.

number of children suffering from developmental disturbances, neglect and abuse are reduced compared with the children born of drug dependent mothers in Copenhagen before Family Center was established (Tables 8).

As a result of the good outcomes of mothers and babies

and the long experience of Family Center of Copenhagen, the Danish Government has decided to establish Family Centers all throughout Denmark during the years 2008-2012. (Table 9)

With the funds granted by the Danish Government, Family Center in Copenhagen has commenced a research program which includes a cross-sectional follow-up study of 196 children who are 12-14 years of age. There will also be an evaluation of the multidisciplinary interventions for the pregnant women and their children who participated in Family Center from 1993 –2004 (1400 pregnant women and 1200 children).

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4. Medication Assisted Pregnancies in Norway. The Guideline Process and the Norwegian Key Questions

Gabrielle Welle-Strand

Medication Assisted Treatment (MAT) started in Norway in 1991. By the end of 2007 there were 4550 patients in treatment, 39 % with buprenorphine (Subutex(r) or Suboxone(r)) and 61 % with methadone. Approximately one third of the patients were women, mostly in child bearing age. Approximately 160 women have given birth to babies while they were in MAT from 1996 up to now. The last 3 years between 25 and 35 babies have been born every year to women in MAT.

Concerning heroin dependent pregnant women, it is still common to medically withdraw or taper them off the opiates with methadone or even none-opioid medications during pregnancy. Qualified in-patient treatment for pregnant women and for the families after birth is available in most regions in Norway, and the whole family can stay there during the entire pregnancy and until the child is 1-2 years old. Norway also has had a law since 1996 making it possible to compulsory treat pregnant drug or alcohol abusing women. Approximately 35-50 women are treated according to this law every year and most of these women are illicit drug users. Pregnancy is not an indication in Norway for starting MAT in heroin dependent women, unlike many other western countries and as stated in the up-coming WHO Guidelines on opioid dependence [4].

The present recommendations for treating pregnant MAT patients in Norway are: Family planning is part of the program and pregnancies are discouraged for unstable patients. When a woman becomes pregnant, thorough information on pregnancy and MAT-issues are given to the woman and her partner. These women and families need long-time multidisciplinary follow-up. No drug use is tolerated for pregnant MAT-patients and couples responsible for children. Alternatives concerning the pregnancy will be discussed, for example the possibility of tapering off the medication and/or getting more extensive treatment, either out-patient or in-patient. The main policy is that methadone or buprenorphine should be continued throughout the pregnancy and the lowest efficient dose of the medication should be administered. Methadone used to be the drug of choice because it is well documented to be safe in pregnancy, but the evidence for the safety of buprenorphine is also good. If tapering off is to be conducted, it should be done gradually between week 14 and 32 of the pregnancy and a possibility of in-patient treatment should be available when needed. If the woman gets very abstinent, the dose of the medication should be stabilized and if necessary, increased. Towards the end of the pregnancy it is recommended to split the

dose of the medication.

A counselling and coordinating group is supporting each patient in MAT and when a woman becomes pregnant, the group will be supplemented by professionals responsible for the follow-up of the pregnancy. Prenatal visits are provided either by a midwife or a doctor, both in the municipality and at the hospital where the baby will be born. There will be close cooperation with the obstetric and paediatric ward. Urine tests for all drugs and alcohol will be taken 1-2 times a week and methadone concentrations will be taken once a month. The follow-up is primarily out-patient, but if necessary, in-patient treatment can be provided. After birth, the babies are transferred to a paediatric ward. In Oslo, many families stay at a specialised institution (Aline) for 2- 6 weeks after the hospital stay. Aline is for babies and families with special needs and the parents will learn to care for their abstinent baby during their stay and other parenting skills if needed.

We performed a national evaluation of women who had babies in MAT from 1996 to 2003. The evaluation was undertaken in 2004 and we managed to trace almost all women in MAT who had given birth during this period through our network of regional contacts. A standardised questionnaire was made in close cooperation with other specialists in the field covering variables used in the international literature. The weaknesses of this evaluation are: There were relatively few patients interviewed, they came from different parts of the country with different treatment philosophies, many different professionals filled in the questionnaires and it was not possible to get hold of all the information for all the respondents. The evaluation covered 56 babies and 55 pregnancies, as there was one pair of twins. 51 women were involved, three women had two children and one woman had three children during the period. The mean age of the mothers at birth was 31.7 years, ranging from 22 to 40 years of age. 59 % of the respondents had older children, on average 1.8, ranging from 1 to 4 older children. Most of the women did not have custody of these older children. 37.5 % of the partners were in MAT and 77 % of all partners had no current drug abuse problem. 77 % of the women were in MAT prior to this pregnancy, on average 16 months before they conceived, of those 36 received methadone and 8 buprenorphine. 21 % of the women started MAT in the pregnancy, 5 on methadone and 6 on buprenorphine.

The last month before the pregnancy was confirmed, 52 % of the women had all their urine screens negative for all drugs and alcohol, 7 % had one to two positive tests and 18 % had more than three urine screens positive. The average number of cigarettes at this stage was 17.2 a day and there were only two non-smokers. The last month before birth, 75 % of the women had no positive urine screens, 9 % had one-to two and 7 % had more than three positive urine screens. The number of cigarettes smoked daily was reduced to 11.7 and there were still only two

no-smokers. A positive urine screen could be positive only for cannabis, for example. In conclusion, there was very little abuse of drugs during these pregnancies, but there was a lot of nicotine exposure for the foetus.

The average methadone dose was 97.9 mg (range 30 to 160 mg) the last month before the pregnancy was confirmed and the average through serum methadone was 706 nmol/l (range 297 to 1100). The recommended serum level is ranging from 600 to 1200 nmol/l. The last month before birth the average methadone dose was 93.3 mg (range 0 to 240 mg) and the average serum methadone was 505 nmol/l (150 to 1399). This shows that there was a great variability in the dosages at birth, two women tapered down to 0 before birth, while some women increased their dose during pregnancy.

There were 66 % boys and 32 % of girls in the sample. The average gestational age was 38.1 weeks, ranging from 29 to 42 weeks. 21 % of the babies were preterm, meaning babies born before the 37th week of pregnancy. The birth weight for all the babies averaged 2927 g (1460 to 3745), the "methadone babies" weighed 2870 g (1460 to 3700 g) and the "buprenorphine babies" weighed 3126 g (2300 to 3745 g). 12 babies had low birth weight, meaning they weighed less than 2500 grams at birth. 48 % of the babies needed medication because of Neonatal Abstinence Syndrome (NAS). 48 % of the "methadone babies" needed treatment for an average of 46.2 days and 50 % of the "buprenorphine babies" needed treatment for an average of 31 days.

We also investigated the present situation for the families. The children were on average two years of age, ranging from 0.2 to 7.9 years. 38 % of the children lived with both their parents, 30 % were living with their mother and 1.8 % lived with its father. 23 % of the children had been put in foster care. Two children of the same mother had died due to Sudden Infant Death Syndrome. Of the 39 children who lived with one or both their parents, 85 % of the mothers had no sign of drug abuse, while 13 % of the mothers used some benzodiazepine. Of the 13 children who were placed in foster care, 46 % of their biological mothers were using drugs to a varying degree.

The Norwegian Directorate of Health has been commissioned by the Ministry of Health to make National Guidelines and Recommendations for the pregnant women in Medication Assisted Treatment and the follow-up of the children and families until school age. The reason for this is partly because the current recommended policy is not followed nationwide. There are variable treatment practices in different parts of the country concerning dosing policies, tapering-off medication, the degree of in- and outpatient treatment offered, the treatment of NAS and the policies concerning breastfeeding. There is also a lot of political, professional and public interest in this issue and the Norwegian parliament spent an hour discussing tapering-off in pregnancy less than two years ago. There is also a lack of knowledge about pregnancies and MAT amongst professionals from different disciplines

and the women and children suffer varying degrees of stigmatization. The aim of the guideline process is to give clear and knowledge based recommendations for the whole period from conception until the child starts school. Our knowledge base is knowledge based on research (evidence), knowledge based on experience (the project group of experts and the reference groups) and the users' knowledge. This knowledge has to be put into a Norwegian context. Most of the research is from US and is not always relevant for Norwegian settings [2, 3].

The Directorate of Health is responsible for the guideline process. A project group of experts was appointed in the autumn of 2007 consisting of two doctors and one psychologist from addiction treatment, one obstetrician, one midwife, one paediatrician, a general practitioner, a social worker, four representatives for the child custody services at different levels, one child psychiatrist, one developmental psychologist and a user's representative. We have asked the Norwegian Knowledge Centre to do a review of the relevant literature. One problem we are encountering is that the search of literature focuses mainly on RCTs and other controlled studies. This has the consequence that studies focusing on the developmental aspects have been left out, an issue we have to address in our ongoing work. We also will have reference groups' meeting twice during the guideline process and we will arrange a separate meeting on the treatment of Neonatal Abstinence Syndrome and also a separate meeting to get the views from many of the users. We aim at a transparent process, where drafts are put out on our web-page, welcoming anybody to comment. When the final draft is ready, we will have a formal consultative round among bodies entitled to comment. The plan is to finish the guideline process by the summer of 2009.

In November 2007 the Directorate arranged an Advisory Conference with International and National Experts. Each of the Norwegian key questions was addressed by an international and a national expert, followed by a discussion in plenary on each topic. The Norwegian key questions addressed at the conference were:

- * What should be the aim of Medication Assisted Treatment in pregnancy?
- * What should be the policy concerning tapering-off during pregnancy?
- * Should methadone or buprenorphine be used during pregnancy?
- * How should the recommendations for breast-feeding be?
- * How and by which hospitals should NAS be treated?
- * What are the long-term results of children born to mothers in MAT?
- * How should the follow-up of the children and family be done in a Norwegian setting?

The project group of experts went on a study-trip to the MATER project in Philadelphia, the CAP project at John

Hopkins Hospital in Baltimore and to the Comprehensive Health Service Centre in New York City. Several of the group members have previously visited several relevant clinics in Copenhagen and Vienna.

There is interesting research going on in Norway in this field at the Centre for Addiction Research at the University of Oslo. Research on the whole cohort of approximately 160 families has commenced. Data is being collected on the pregnancies and birth outcomes. The second part of the study will be a follow-up study, focusing on how the children and families are doing. The 2005 and 2006 cohort has been followed prospectively from the pregnancy and up to the age of 2 years by Monica Sarfi and Britteliise Bakstad [1]. The treatment group consists of 38 families with mothers in MAT and there is a similar normal control group. The mother and father are interviewed during the pregnancy and the child and the mother-child dyad is being assessed and the parents fill out questionnaires at 3, 6, 9, 12 months and at 2 years of age. A follow-up is presently being planned for the 4 year old children. Another research group led by Vibeke Moe is doing similar investigations on a group of mothers who have used opiates illegally during pregnancy and a group of mothers with psychosocial problems.

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Conflict of Interest

The author has no relevant conflict of interest to report in relation to the present report.

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